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<b>(21) International Application Number:</b> PCT/US86/01893 <b>(22) International Filing Date:</b> 11 September 1986 (11.09.86) <b>(31) Priority Application Number:</b> 781,147 <b>(32) Priority Date:</b> 27 September 1985 (27.09.85) <b>(33) Priority Country:</b> US  <b>(71) Applicant:</b> THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 2199 Addison Street, Berkeley, CA 94720 (US).  <b>(72) Inventors:</b> GUY, Richard, H. ; 342 Ardenale Drive, Daly City, CA 94014 (US). SZOKA, Francis, C. ; 45 Mendosa Avenue, San Francisco, CA 94116 (US). KNEPP, Victoria, M. ; 375 Carl Street, Number 4, San Francisco, CA 94117 (US). WESTER, Ronald, C. ; 8 Lockoley Avenue, 2D, San Francisco, CA 94122 (US).		<b>(74) Agents:</b> DEHLINGER, Peter, J. et al.; Ciotti & Murashige, 545 Middlefield Road, Suite 200, Menlo Park, CA 94025 (US).  <b>(81) Designated States:</b> AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> LIPOSOME TRANSDERMAL DRUG DELIVERY SYSTEM  <b>(57) Abstract</b> <p>A transdermal drug release device for releasing a physiologically active, lipophilic drug to a skin surface at a selected, substantially constant rate over a period of at least about 24 hours. The device includes an aqueous-phase matrix having a surface adapted to be placed against the skin surface, and, embedded within the matrix, liposomes containing the drug in entrapped form and composed of lipid components which are selected to produce such drug release rate. In one embodiment, the matrix contains a water-soluble drug in free form, and then entrapped lipophilic drug is a drug transport agent designed to facilitate transdermal uptake of the water-soluble drug.</p>		

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LIPOSOME TRANSDERMAL DRUG DELIVERY SYSTEM1. Field of the Invention

5 The present invention relates to transdermal drug delivery devices.

2. Background of the Invention

10 The delivery of drugs via the skin to produce systemic effect is attractive for many reasons. Depending on the site of transdermal drug administration, first-pass metabolism by the liver may be avoided. Often the drug can be administered close to the site of action, allowing a more localized drug action. Because a steady, sustained concentration of  
15 drug at the site of action can be maintained, dosing frequency and dose magnitude can be reduced, with fewer side effects and better patient compliance.

A variety of transdermal drug delivery devices have been proposed heretofore. One general type of  
20 transdermal device consists of a matrix reservoir containing a drug in free form, and one or more microporous walls which limit the rate of drug diffusion out of the matrix. For example, United States Patent No. 4,336,243 describes a nitroglycerine patch in which  
25 the drug is contained in a cross-linked silicon matrix formed of microporous, cross-linked walls. In the transdermal devices disclosed in United States Patents Nos. 4,286,592, 4,060,084, 3,371,683, and 3,596,122, the rate of drug release from the matrix is controlled by a  
30 drug release barrier placed between the matrix and skin.

Transdermal devices of the type just described have a number of limitations. The rate of drug diffusion through the microporous wall can vary widely, depending on drug size and solubility. Therefore,

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considerable design work may be required to construct a diffusion barrier having desired permeability properties for a given drug. Also, where the diffusion barrier is a single membrane, small variational defects in the membrane can lead to significant variations in drug release rate. The devices are best suited to water-soluble drugs which can be dispersed in high concentration throughout a hydrated matrix.

In another type of known transdermal drug delivery device, the drug is encapsulated in microcapsules which are distributed throughout a drug matrix. The microcapsule walls are permeable to passage of the drug, and act to control the rate of drug release from the device. Devices of this types are disclosed in U.S. Patents Nos. 3,598,123, 3,797,494, and 3,464,413. Typically the drug is a water-soluble drug encapsulated in a polymer-shell microcapsule.

As in the diffusion-barrier devices mentioned above, considerable design work may be required to discover the proper material and cross-linking conditions which produce a microcapsule with the desired permeability characteristics for a given drug. Further, drug encapsulation and diffusion-barrier control are generally impractical for lipophilic drugs.

### 3. Summary of the Invention

It is a general object of the invention to provide an improved transdermal drug release device which overcomes above-mentioned limitations in the prior art.

A specific object of the invention is to provide such a device for releasing a lipophilic drug at a selected, substantially constant release rate over a period of at least about 24 hours.

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Another object of the invention is to provide a transdermal device for delivering a water-soluble drug under conditions which promote transdermal uptake of the drug.

5           Still another object of the invention is to provide a method of achieving a selected, substantially constant release rate of a lipophilic drug in a transdermal device.

10           The liposome drug release device, or patch of the invention includes an aqueous-phase matrix having a surface adapted to be placed against the skin surface. Liposomes embedded within the matrix and containing an entrapped lipophilic drug are formulated to produce a selected, substantially constant rate of drug release  
15           for a period of at least about 24 hours. The concentration of liposomes in the matrix is preferably between about 5 and 25 percent by volume, and the major portion of drug in the matrix is partitioned initially in the liposome bilayers.

20           In one embodiment, the matrix contains a water-soluble drug in free form, and the entrapped lipophilic drug is a drug-transport agent effective to facilitate transdermal uptake of the water-soluble drug. The device may include a diffusion barrier to  
25           control the rate of release of water-soluble drug from the matrix, such that both the water-soluble drug and uptake agent are delivered from the device at relatively constant, selected release rates.

30           In another aspect, the invention includes a method of achieving a selected, substantially constant rate of release of a lipophilic drug from an aqueous-phase matrix over a period of at least about 24 hours. The method involves entrapping the drug in liposomes containing phospholipid components which are

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selected to produce such a rate of drug release from the liposomes into an aqueous medium, and embedding the liposomes in the matrix.

5 These and other objects and features of the present invention will become more fully apparent from the following detailed description of the invention, when read in conjunction with the accompanying drawings.

#### Brief Description of the Drawings

10 Figure 1 is a schematic sectional view of a transdermal drug delivery patch constructed according to one embodiment of the invention;

15 Figure 2 is a sectional view of a transdermal drug delivery patch constructed according to another embodiment of the invention;

20 Figures 3A and 3B are, respectively, graphs of percent progesterone (PG) release per hour in a transdermal patch containing free PG, over a 24 hour period, and cumulative percent PG released from the patch over the same time period;

Figures 4A and 4B are graphs showing PG released per hour and cumulative PG released, respectively, for a transdermal patch in which PG is entrapped in egg phosphatidylcholine (PC) liposomes;

25 Figures 5A and 5B are graphs showing PG released per hour and cumulative PG released, respectively, for a transdermal patch in which PG is entrapped in dipalmitoyl phosphatidylcholine (DPPC) liposomes;

30 Figures 6A and 6B are graphs showing PG released per hour and cumulative PG released, respectively, for a transdermal patch in which PG is contained in oil emulsion particles;

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Figure 7 is a plot of the relationship between percent PG release and square root of release time for an egg PC liposome transdermal patch;

5 Figures 8A and 8B are graphs showing respectively, the percent dose of PG per hour and cumulative PG delivered across full-thickness skin, for a transdermal patch in which PG is contained in free form;

10 Figures 9A and 9B are graphs showing, respectively, the percent dose of PG per hour and cumulative PG delivered across full-thickness skin, for a transdermal patch in which PG is entrapped in egg PC liposomes; and

15 Figures 10A and 10B are like Figures 9A and 9B, respectively, for a patch in which PG is entrapped in DPPC liposomes.

#### Detailed Description of the Invention

##### 20 1. Liposome Transdermal Patch

The transdermal drug-release device, or patch, of the invention includes an aqueous-phase matrix, and embedded within the matrix, liposomes containing a lipophilic drug in entrapped form. The liposomes are  
25 composed of lipid components and preferably phospholipid components which are selected to produce a desired rate of drug release from the matrix. According to an important aspect of the invention, the drug-release rate is substantially constant for at least about 24 hours,  
30 and up to two weeks or more, depending on the liposome composition.

The lipophilic drug may be a systemically active drug which is effective at relatively low blood levels, when delivered over a prolonged period. Such

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drugs include birth control steroids, such as mestranol, norethynodrel, ethanyl estradiol, norgestrel, estradiol, progesterone, and norethindrone; other steroids, such as testosterone; anti-inflammatory drugs, such as cortisone and triamcinolone, analgesic drugs, such as morphine and codeine; nitrates, such as nitroglycerine and isosorbide dinitrate; anti-hypertensives, such as furosamide, chlorothiazide, minoxidil and propranol; anti-depressants, such as protriptyline; cardiovascular agents, such as quinidine, disopyramide, and clonidine; fat-soluble vitamins, such as vitamin A and D; prostaglandins; prostacyclines; and calcium channel blockers, such as nifedipine.

Alternatively, the drug may be one whose primary site of action is the site of topical administration. Drugs of this type include anti-inflammatory agents, antibiotics, analgesics, and local anesthetics, such as novacaine, and lidocaine.

In another general embodiment of the invention to be described below, the lipophilic drug is a drug-transport agent designed to facilitate transdermal uptake of a water-soluble drug which is present in free form in the matrix and delivered from the matrix concurrently with the drug-transport agent. Exemplary transport agents include a variety of aliphatic, cycloaliphatic and aromatic compounds, such as those named in U.S. Patent No. 3,797,494. One preferred type of drug-transport agent is selected from a class of azacyclo pentane- and heptane-ones, such as those disclosed in U.S. Patents Nos. 4,316,893 and 3,989,816.

According to an important feature of the invention, the rate of drug release from the matrix is controlled by the rate of drug exchange between liposomes and the surrounding aqueous medium. In

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particular, studies conducted in support of the invention, and reported in Section II below, show that liposomes have the capability of releasing (exchanging) drug at a relatively constant rate, independent of liposome drug concentration, and that the rate of drug release, or exchange, can be controlled, within broad limits, by varying the lipid composition of the liposomes.

In order to achieve liposomal control of drug release, it is necessary that a major portion of the drug in the matrix be partitioned initially in the lipid phase of the embedded liposomes. Partitioning of the drug between the lipid (liposome bilayer) and aqueous phase (the non-liposomal bulk aqueous phase) is determined by the lipid/aqueous partition coefficient of the drug and the volume percent of liposomes in the matrix. For example, in a device in which the liposomes constitute 10 percent of the total matrix volume, a drug having a liposome/aqueous phase partition coefficient of 10 will partition in roughly equal amounts between the liposomes and bulk aqueous phase of the matrix. At a drug partition coefficient of 1000, about 99% of the drug will be entrapped. The partition coefficient of the drug and the volume percent of liposomes in the matrix are preferably selected to insure that at least about 50% and more preferably, 80% or more of the drug is contained in the liposomes at initial drug-release conditions. Assuming that the liposomes make up, at most, about 25% of the matrix volume, the lipophilic drug used in the invention should therefore have a partition coefficient of at least about 4.

The partition coefficients of many drugs have been determined for two-phase oil water solvent mixtures, such as an octanol/water mixture (see, for



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example, Yalkowsky, S.H., et al, Pharma. Sci. 72:866 (1983)). The drug partition coefficients determined using simple oil/water mixtures are useful in comparing the relative lipophilic character of different drugs.

5 However, the actual partition coefficient of a drug in liposomes depends on several factors which affect the hydrophobicity of the liposome bilayer region and degree of lipid packing in the liposome bilayer. Although actual liposome/water partition coefficients for  
10 selected liposomes can be measured, it is usually simpler to measure directly the drug release rates of a selected drug with respect to liposomes having different lipid compositions, and at different liposomes concentrations, and from these measurements, to  
15 determine (a) if the drug is sufficiently lipophilic to show liposome-controlled drug release and (b) if so, the liposome composition and concentration which will produce the desired drug release rate in the device.

Considering the selection of suitable liposome  
20 components, co-owned U.S. patent application for "Liposome Inhalation System and Method", Serial No. 737,221, filed 25 March 1985, describes an in vitro system for determining the rate of release of liposome-entrapped drugs, as a function of liposome  
25 lipid composition. The system was used to examine 40 different phosphatidylcholine (PC) lipids and lipid mixtures to determine the effect of acyl chain length, degree of saturation, polar head group charge, and presence of cholesterol on the release of metaproteranol  
30 sulfate (MPS) from liposomes. Although MPS is a relatively water-soluble drug, studies conducted in support of the present invention, and reported in Example III below, indicate that the general finding for MPS also apply to a highly lipophilic drug, such as

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progesterone (PG). Briefly, it has been found with both drug types that the most important compositional factor for drug release rates is phospholipid acyl chain length and degree of saturation, with more fluid acyl chains (shorter and/or more unsaturated) giving higher release rates. Thus, in Example III it is seen that liposomes formed with egg PC, which includes a mixture of relatively short-chain and unsaturated lipids, have a drug release rate about six times higher than that of liposomes formed with dipalmitoylphosphatidylcholine (DPPC), a relatively long-chain, saturated lipid. Pure phospholipids and phospholipid mixtures with a variety of acyl chain moieties are commercially available or can be isolated or synthesized by known methods.

The effect of cholesterol on drug release rate in egg PC liposomes has also been examined (Example III). Liposomes containing PC and cholesterol, at a 2:1 mole ratio, showed substantially the same PG release rate as did pure egg PC liposomes (about 1% total drug release per hour). These results are consistent with earlier studies on release of MPS from liposomes, which showed that cholesterol only slightly increased drug release in egg PC liposomes. However, the MPS studies did show that cholesterol can significantly increase drug-release in liposomes whose phospholipid components contain long-chain, saturated acyl groups.

The lipids forming the liposomes may, of course, include phospholipids and sterols other than the model lipids used in the above-mentioned studies and Examples, and may also include other types of lipids, such as glycolipids and sphingolipids, which are compatible with liposome formation. A list of lipids which are used commonly in liposome formation is given on page 471 of Szoka, F., Jr., et al, Ann. Rev. Biophys.

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Bioeng. 9:467 (1980). The liposomes may also be formulated to include various types of drug-protective or lipid-protective agents, such as the antioxidant  $\alpha$ -tocopherol, which was included at a 0.6 mole percent in the liposomes described in the examples.

5 The liposomes may be prepared by a variety of techniques, such as those detailed in the above-cited Szoka et al reference. A simple lipid-hydration procedure for producing multilamellar vesicles (MLVs) is  
10 generally suitable. In this procedure, a mixture of vesicle-forming lipids and the drug are dissolved in a suitable organic solvent or solvent mixture, then evaporated in a vessel to form a thin film. Hydrating the thin film with an aqueous solution, over a period of  
15 at least about 1 hour, produces multilamellar vesicles (MLVs), with sizes typically between about 0.1 to 10 microns.

Although the drug is preferably incorporated initially into the lipids forming the vesicles, as  
20 above, it may also be diffused into preformed liposomes. If necessary, the drug diffusion step can be carried out in the presence of a mild detergent, such as deoxycholate, to facilitate drug exchange with the liposomes. The detergent can be removed by dialysis  
25 after liposome uptake.

The amount of drug which is included in the lipid-forming vesicles is that calculated to produce a selected total drug concentration in the transdermal device. The amount of drug that can be incorporated  
30 into the transdermal device is limited by the amount of drug that can be stably incorporated into liposomes, the maximum allowed concentration of liposomes in the matrix and patch size. Typically, vesicle-forming lipids can form stable liposomes in the presence of between 1-5

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mole percent drug. For some drugs, such as a variety of sterols, the drug concentration can be as high as 40-50 mole percent without significant membrane instability. In general, the drug to lipid ratio can be safely increased until an increase in the rate of drug release is observed in the liposomes. The increase drug-release rate signals drug-saturation of the liposomes and membrane instability.

10 The maximum concentration of liposome which can be embedded in the matrix will depend on the nature of the material forming the matrix and the method of matrix formation. Generally, the concentration of liposomes in the matrix will be between about 5% and 25% based on the total liposome volume per total matrix volume.

15 The matrix can be formed of any dermatologically acceptable gel or cross-linked polymer material which is compatible with an aqueous medium, and capable of gelling or forming cross links under conditions, particularly temperature conditions, which do not disrupt liposomes. A variety of polymers and polymer mixtures, which are suitable are listed in U.S. Patent No. 3,797,494, columns 14 and 15. Also disclosed in this patent are a number of gel-forming polymers, such as cellulose derivatives, which are useful in forming the matrix. One preferred matrix material used in the device described in Examples II-IV, is the polysaccharide agarose.

30 To form the matrix, liposomes are added to an aqueous suspension or solution of the matrix forming material, and the mixture is then cross-linked or gelled to produce a rigid or semi-rigid matrix structure having immobilized liposomes embedded throughout. In the case of a polymer type matrix material, the cross-linking step may involve adding a chemical catalyst, and/or

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light-induced cross-linking. For example, an acrylamide polymer matrix can be formed by cross-linking acrylamide, either by addition of a free-radical generator such as ammonium persulfate, or by light-induced cross-linking in the presence of a photosensitizer such as riboflavin. Methods for cross-linking polymers under suitable temperature conditions are well known. The material is cross-linked in a suitable mold.

A gel matrix is formed typically by heating gel material in an aqueous medium to its solution temperature, cooling the solution to somewhat above its gelling temperature then mixing the material with a selected volume of liposome suspension. The concentration of the gelled material is selected to provide a relatively firm, shape-retaining structure after dilution with the liposome suspension. Typically, the final gel concentration is between about 1%-5% w/v. The liposome/gel material is poured into a mold and cooled to form the matrix. Example II below describes the preparation of liposome patches by mixing a 4% agarose solution at 67°C with an equal volume of liposome suspension and allowing the mixture to gel by slow cooling.

The matrix is preferably covered on one side by an impermeable cover, such as metal foil or the like, to prevent drying out during use. The cover can be attached by adhesives or the like after matrix formation. Alternatively, the cover can be bonded to the matrix during the molding step, by pouring the still-liquid matrix material over the cover in a mold.

Figure 1 is a schematic, sectional view of a liposome drug-delivery device 10 prepared according to the invention. An aqueous-phase matrix, indicated at

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12, contains liposomes, such as those shown at 14, embedded throughout. The liposomes serve as a reservoir for a lipophilic drug, a portion of which is available in free form, as indicated at 18. The lower surface of the matrix in the figure defines a drug-release surface 20 adapted to be placed against a skin surface for transdermal drug delivery. The upper surface is sealed with an impermeable cover 22. Although not shown, the cover extends beyond the edges of the matrix, and is adhesive backed in its extending edge regions, allowing the device to be adhesively attached to a skin surface.

An alternative embodiment of the invention, for use in delivering a water-soluble drug, is illustrated at 24 in Figure 2. In operation, this device releases both a water-soluble drug, which is contained in free form in the matrix, and a lipophilic drug-transport agent of the type mentioned above, which acts to increase transdermal uptake of water-soluble molecules. The transport agent is contained in liposomes, such as those at 26, and these are embedded in an aqueous-phase matrix 28, as in device 10 above. The device is formed as above, except that the water-soluble drug, indicated at 29, is included in the polymer or gel material used in forming the matrix. Exemplary water-soluble drugs include antihistamines, such as dimenhydrinate, diphenhydramine, chlorpheniramine, and ephedrin; anti-motion drugs, such as scopolamine; antibiotics, such as penicillin; and tranquilizers and other nervous disorder drugs, such as dopa.

Device 24 has a cover 30 protecting its upper surface against dehydration, and also has a diffusion-barrier membrane 32 covering its lower drug-release surface. Membrane 32 functions to limit the rate of release of the water-soluble drug from the

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matrix, preferably at a release level which is compatible with the release rate of the lipophilic drug-transport agent. The diffusion-limiting membranes described in U.S. Patents Nos. 4,286,592; and 3,598,123, for use in limiting the rate of passage of water-soluble membranes are generally suitable.

### III. Drug-Release and Uptake Characteristics

This sections examines the drug-release characteristics of liposome transdermal devices and the ability of the devices to modulate drug uptake by skin. Drug release rates were measured as detailed below in Example III. Briefly, a PG-liposome patch, prepared as in Section I, was placed in one chamber of a two-chamber diffusion cell. The second confronting chamber was filled with a suitable receptor liquid to serve as a reservoir for released drug. Receptor fluid was flowed through the reservoir at a suitable rate, and the reservoir discharge sampled every hour for released radioactive PG. Transdermal patches containing PG in three different liposome formulations and in free and emulsion form were compared. One liposome formulation containing egg PC, whose fatty acyl composition is 16:0 (42%), 18:1 (28%), and 18:2 (16%), i.e., both relatively short (16:0) and unsaturated (18:1 and 18:2) acyl chains. A second liposome formulation contained egg PC/cholesterol, at a 2:1 mole ratio. The third formulation contained pure DPPC, whose palmitoyl chains (18:0) are relatively long and unsaturated.

Figure 3A shows the levels of drug release from the free-drug patch measured at 1 hour intervals over a 24 hour period, where the radioactivity measured at each time point is expressed as percent of total radioactivity in the patch. As seen from the figure,

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about 20% of the total free drug was released in the first hour, and drug release levels declined sharply over the first 15 hours. When the data is plotted as cumulative percent dose, the curve shown in Figure 3B is obtained. As seen, nearly 90 percent of the free drug is released in the first 24 hours.

Drug release characteristics of a liposome patch prepared with egg PC lipids are shown in Figure 4A and 4B. Referring to Figure 4A, the liposome patch released progesterone at a substantially constant release rate of about 1 percent total drug per hour over the 24 hour test period. The plot of cumulative amount released over the 24 hour period (Figure 4B), shows a substantially linear increase in released PG over 24 hours, to about 25% of total drug. Drug-release measurements on the egg PC/cholesterol patch, taken every hour over a 48 hour test period were similar to those for egg PC liposomes. The rate of drug release was 1% per hour over the test period, and about half the drug was released in 48 hours.

The drug release characteristics of the the DPPC liposome patch were also measured over a 48 hour period, with the results shown in Figures 5A and 5B. The percent dose release every hour, plotted in Figure 4A, remained substantially constant, at between about 0.15 and 0.2 percent total drug, over the entire test period. The cumulation of drug dose, plotted in Figure 5B, shows that (a) the drug accumulates in a linear fashion, and (b) the rate of accumulation is about 4% total PG every 24 hours. The drug accumulation rate is that seen for both the egg PC and egg PC/cholesterol liposome patches.

The drug release and accumulation characteristics of a lipid emulsion patch are graphed in



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Figures 6A and 6B, respectively. With reference to Figure 6A, the drug release rate was substantially constant at about 2.5% per hour, for the first 8-10 hours, then declined to about 1% per hour after 24 hours. As seen in Figure 6B, the released drug reached an accumulated level of about 30% of total drug during the first 12 hour period of linear drug release, and a final accumulated drug level of about 50% after 24 hours. In Figures 3A-6A, the error bars are standard deviations for 5-6 individual tests.

The data from Figures 3-6 are summarized in Table I below. The lipid composition in the patch tested is indicated at the left in the table. The two middle columns show the approximate drug release rate/hour, expressed as percent total drug, and the time over which the drug release rate is substantially linear. The final column shows the cumulative drug levels after 24 hours.

Table I

Lipid	Drug Release Rate/Hour	Linear (hours)	Cumulative (24 hours)
Free PC	--	--	90%
Emulsion	2.5%	8-10	50%
Egg PC	1%	>24	25%
Egg PC/CH	1%	>48	25%
DPPC	0.16%	>48	4%

The drug release curves in Figures 3B-6B were compared with theoretical drug release curves predicted from mathematical modeling, using Fisk's second law of diffusion with appropriate boundary conditions. A

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linear cumulative percent dose vs time, as was observed for the liposome drug release patches, is consistent with a model in which drug release in the system is modulated by slow interfacial transfer from the lipid bilayer into the aqueous receptor phase, rather than by diffusion through the matrix. According to this model, the liposomes act as a reservoir of drug within the matrix, with drug release from the reservoir being controlled by the partitioning of the drug in the matrix rather than by total drug concentration. By contrast, classic release behavior involving matrix diffusion predicts that the total percent drug release will be directly proportional to the square root of time, i.e., the system will show a strong time dependence related to a decreasing drug concentration in the matrix. The percent release vs square root of time for the EPC liposome patch is plotted in Figure 7. The linear relationship expected for a matrix diffusion process was not observed.

The ability of the above liposome transdermal patches to modulate transdermal drug uptake across full-thickness skin was also examined. Drug uptake through the skin was measured by placing a piece of full-thickness mouse skin between the chambers in a two chamber diffusion cell, and measuring release of drug (PG) into a flow-through reservoir, as above. The study compared drug uptake by skin from patches containing either free PG, PG in egg PC liposomes, or PG in DPPC liposomes. Details of the method are given in Example IV.

Figure 8A shows the levels of PG delivered transdermally into the lower reservoir from the free-drug patch, measured at 1 hour intervals over a 48 hour period. The radioactivity measured at each time

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point is expressed as percent total radioactivity in the patch. As seen, the amount of drug penetrating the skin barrier reached a maximum of about 0.4%-0.5% within 6-8 hours, and remained at this level throughout the test period (only the first 40 hours of the test period are shown). The skin sample variation in drug-release rates is indicated by the standard deviation bars in the figure. When the drug-release data is plotted as cumulative percent dose, the curve in Figure 8B is obtained, showing that about 25% of the total drug penetrated the skin barrier in the 48-hour test period.

The rate of transdermal PG uptake, when the drug is released from an egg PC liposome patch, is shown in Figure 9A. The rate of drug transport across the skin reached a level of about 0.2% per hour within about 16 hours, then substantially plateaued over the next 40 hours. The plot of accumulated drug over time (Figure 9B), when extrapolated to 48 hours, showed that about 10% of the total drug was delivered over a 2-day period. The liposome patch thus modulates, by a factor of 2-3, the rate of transdermal drug uptake, compared with a diffusion-limited (free-drug) transdermal device.

It is known that transdermal uptake varies widely among individuals, and this variation probably accounts for the relatively large standard deviations observed among the 4 test-subject skin samples in Figure 8A for progesterone supplied by the free-drug patch. A comparison of Figures 8A and 9A shows that the liposome drug delivery patch, which supplies progesterone at a controlled, substantially constant rate, significantly reduces this variation.

The ability of a liposome transdermal device to modulate transdermal uptake and reduce individual-specific variations in drug uptake is seen more

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strikingly in Figures 10A and 10B, which plot transdermal uptake characteristics observed with a DPPC liposome patch. Figure 10A shows that transdermal uptake increased over the first 8-16 hours, then plateaued over the next 24 hours at about 0.03% per hour, with a standard deviation of about .01% total dose. Total drug uptake was about 1.35% after 48 hours.

The results of the transdermal uptake studies are summarized in Table II below. The drug transport rate is the steady-state level observed after several hours, and the standard deviation is an approximate average of the standard deviation observed during the steady-state period. The roughly five-fold difference in drug transport rates between the egg PC and DPPC patches is consistent with the difference in the drug-release rates (Table I) between the two patches.

Table II

<u>Lipid</u>	<u>Drug Transport (rate/hr)</u>	<u>Standard Deviation</u>	<u>Cumulative (24 hr)</u>
Free PC	0.4%	~.2%	25%
Egg PC	0.2%	~.1%	10%
DPPC	0.03%	~.02%	1.35%

The ability of the liposome transdermal patch to control drug bioavailability in vivo has been confirmed in tests with rhesus monkeys. The tests were designed to determine estradiol transdermal bioavailability by cumulative tuition excretion following drug administration. The drug/liposome patch was applied for either 24 or 48 hours. The bioavailability was about 1% total drug for the 24 hour

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application and roughly twice that for the 48 hour application. In both cases, the drug level remained constant for 24 hours after the patch was removed. The same quantity of drug administered topically in free  
5 form (as a topical solution) gave about 10% drug level after 24 hours and the drug level fell rapidly during the 24-48 hour period. These results confirm that (a) the liposome drug delivery device functions to deliver a drug transdermally at a controlled rate and (b) the  
10 total amount of drug delivered increases linearly with time of application.

From the foregoing it can be appreciated how various objects of the invention are met. The liposome patch is easily constructed and the lipid and matrix  
15 components are stable for periods of several months or more under suitable storage conditions.

The liposome system can be readily adapted to deliver any relatively stable, lipid-compatible lipophilic drug, and the drug release rate can be  
20 readily adjusted by appropriate selection of liposome lipid components and liposome concentration. In addition, where the drug is charged, the salt concentration of the aqueous medium can also be adjusted to alter the partitioning of the drug in the matrix.

25 Since the drug-release rate is largely dependent on drug partitioning across a liposome/water interface, rather than on drug concentration within the liposomes, the device can be designed to produce a controlled, substantially constant rate of drug release  
30 over an extended period. The studies on the DPPC liposome device indicate that a constant drug release for up to 2 weeks is possible. Further, the total amount of drug released, at a selected drug release

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rate, is easily varied by varying drug concentration in the liposomes or the volume of the patch.

The device is able to modulate the rate of drug transport through skin, and the data in Table II indicates that the extent of modulation can be controlled over at least a five-fold range, by selected changes in liposome composition.

The following examples describe several liposome transdermal drug delivery devices and their drug release characteristics. The examples are intended to illustrate, but not limit, the invention.

#### Materials

Phospholipids, at greater than 99% purity, were obtained from Sigma Chem Co (St. Louis, MO); cholesterol, from Sigma Chemical Co. (St. Louis, MO), and C<sup>14</sup>-labeled Progesterone (PG). INTRALIPID was supplied by Cutter Labs (Berkeley, CA). GELBOND backing, an impermeable membrane, and agarose were obtained from FMC Corporation (Rockland, ME).

#### Example I

##### Drug/Lipid Preparations

Lipid solutions containing either (a) pure egg PC, (b) egg PC:cholesterol, at a mole ratio of 2:1, or (c) pure DPPC were prepared to a final lipid concentrations of about 100 mg/ml in chloroform. Each of the solutions (2.5 ml) was combined with about 0.4  $\mu$ Ci C<sup>14</sup>PG in a round bottom flask and the mixture dried to a film under vacuum.

To each flask was added citrate buffered saline, pH 4.5, to a final lipid concentration of about 63 mg lipid/ml, and a final C<sup>14</sup> PG concentration of about 0.1  $\mu$ Ci/ml. The lipid films were hydrated by

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gentle swirling for one hour at 37°C to form suspensions of multilamellar vesicles (MLVs). The suspensions are designated egg PC, egg PC/cholesterol, and DPPC, according to their lipid composition.

5 INTRALIPID, an emulsion of soybean oil in a physiological salt solution, was concentrated to 22 mg lipid/ml. C<sup>14</sup>PG was added to the concentrated emulsion to a final concentration of about 0.5 µCi/ml.

#### 10 Example II

##### Preparing Transdermal Patches

A suspension of agarose in citrate-buffered saline, pH 4.5, was solubilized by heating, then cooled to 67°C.

15 Transdermal liposome patches were prepared by mixing equal volumes of 4% agarose at 67°C and a selected MLV suspension from Example I, and pouring about 1 ml of the warm mixture into a 5 cm square mold. The bottom of each mold was covered with a 16 cm square  
20 piece of GELBOND membrane, with the hydrophilic side of the membrane facing up. The agarose-lipid mixture was allowed to gel by cooling to room temperature. Each patch had a final thickness of about 1.5 mm, and contained a total of about 40 µCi C<sup>14</sup> PG.

25 An INTRALIPID PATCH was similarly prepared by mixing 0.9 ml of agarose and 0.12 ml of INTRALIPID to a final agarose concentration of about 2%. The patch contained 38-40 µ mole lipid and 0.05 µCi C<sup>14</sup> PG.

30 A transdermal patch containing free PG only (nonlipid patch) was prepared by mixing the warm 4% agarose from above with an equal volume of PG in citrate-buffered saline (0.1 µCi/ml). The mixture was poured into a mold and cooled, as above.

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Example IIIDirect Drug-Release Rates: Lipid vs Nonlipid Patches

The rates of drug release from the lipid and nonlipid patches prepared in Example II were measured in a standard glass diffusion cell of the type having separable, confronting chambers. The transdermal patch being tested was placed in the upper chamber, with its free surface facing inwardly. The lower chamber, which served as a liquid reservoir for receiving drug released from the patch, was provided with opposite-side ports for flowing receptor liquid through the lower chamber. In operation, the lower cell was filled with citrate-buffered saline until the free (inwardly facing) side of the patch was completely covered with the reservoir solution. Fresh reservoir solution was flowed through the lower reservoir at about 10 ml/hr. over a 24-48 hour period. The rate of release of radioactive PG was determined by measuring the radioactivity in the 10 ml fractions collected every hour, over a 24 hour period. The samples were counted by standard scintillation counting methods.

The amount of released PG, expressed in percent total PG released per hour is plotted in Figures 3A-6A, discussed above, and the cumulative PG released, over the 24-48 hour test period, in Figures 3B-6B. The error bars on Figures 3A-6A represent standard deviation among 5-6 individual readings.

Example IVTransdermal Drug Release Rates:Liposomal versus Nonliposomal Patches

The rate of transdermal delivery of drug across full-thickness mouse skin was examined for the nonlipid and egg PC liposome transdermal patches in Example II.



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Hairless SKH-HR1 mice were supplied by Temple University Heath Science Center (Philadelphia, PA). Expanses of full-thickness skin, at least 6 cm square, were removed from the abdominal region of the animals and placed between the upper and lower chambers in the glass diffusion chamber described above, so that the skin was in contact with the entire free surface of a drug release patch placed in the upper chamber. The lower chamber was filled with the above citrate-buffered saline until the entire exposed surface of the skin expanse was in contact with the liquid. During operation, receptor liquid was flowed through the chamber at about 10 ml/hr. The 10 ml fractions collected after each hour were counted for radioactivity as above.

The levels of PG transported through the skin, expressed as percent total drug per hour are graphed in Figures 8A-10A for free PG, egg PC liposome, and DPPC liposome patches, respectively. The error bars represent standard deviation among 4 individual skin samples. Figures 8B-10B show the corresponding cumulative drug doses transported through the skin for the three patches studied.

While preferred embodiments of the invention have been described and illustrated, it will be apparent that various changes and modifications can be made without departing from the invention.

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THERE IS CLAIMED:

1. A transdermal drug release device for releasing a physiologically active, lipophilic drug to a skin surface at a selected, substantially constant release rate over a period of at least 24 hours, comprising:

an aqueous-phase matrix having a surface adapted to be placed against the skin surface, and embedded within the matrix, liposomes containing the drug in entrapped form, and composed of lipid components selected to produce such a release rate, at a liposome volume concentration that insures that a major portion of the drug is contained in the liposomes.

2. The device of claim 1, wherein the concentration of liposomes in the matrix is between about 5-25 percent by volume, and at least about 80% of the drug in the matrix is contained in the liposome.

3. The device of claim 2, wherein the drug is selected from the group consisting of nitroglycerine, prostaglandins, prostacyclines, and steroids.

4. The device of claim 2, which is effective to release drug at a relatively high release rate, wherein the liposomes lipid components are selected to include phospholipids with unsaturated acyl chain moieties.

5. The device of claim 4, wherein the liposome phospholipid components include egg phosphatidylcholine.

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6. The device of claim 2, which is effective to supply drug at a relatively low release rate, wherein the liposomes lipid components are selected to include phospholipids with predominantly saturated acyl-chain moieties.

7. The device of claim 1, wherein the matrix is a polysaccharide gel.

8. The device of claim 1, which further includes a hydrophilic drug contained in the aqueous phase of the matrix, and the lipophilic drug is adapted to increase transdermal uptake of the hydrophilic drug.

9. The device of claim 8, wherein the hydrophilic drug is selected from the group consisting of peptide hormones, water-soluble antibiotics, and anti-motion drugs.

10. The device of claim 8, which further includes a diffusion-limiting membrane interposed between the matrix and such skin surface, with the device operatively placed for transdermal drug delivery.

11. In a transdermal drug delivery system in which a physiologically active, lipophilic drug is released from an aqueous-phase matrix onto a skin surface, a method of achieving drug release from the matrix at a selected, substantially constant rate over a period of at least about 24 hours, comprising:

entrapping the drug in liposomes containing a lipid components which are selected to produce such a selected rate of drug release from the liposomes into an aqueous medium, and

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embedding the liposomes in the matrix at a concentration effective to achieve such release rate.

5 12. The method of claim 11, for achieving a relatively high drug release rate, wherein the lipid components are selected to include phospholipids whose acyl-chain moieties are predominantly unsaturated and/or short-chain.

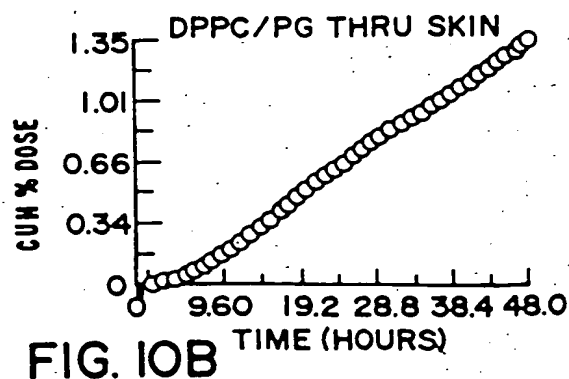
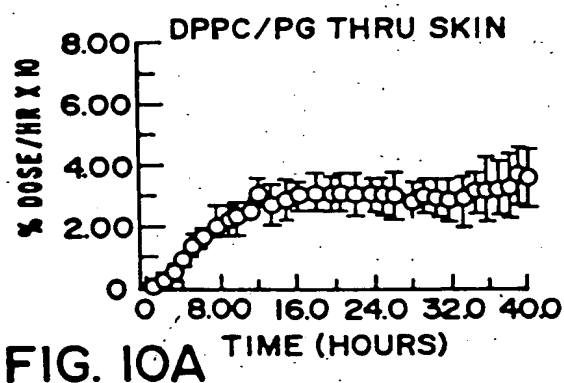
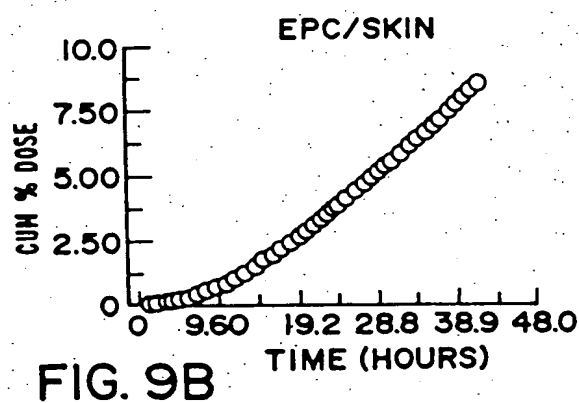
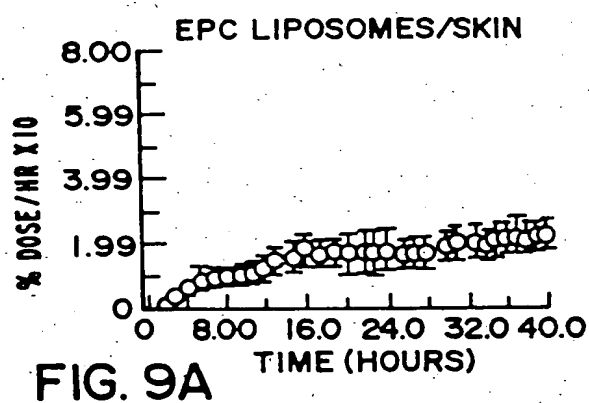
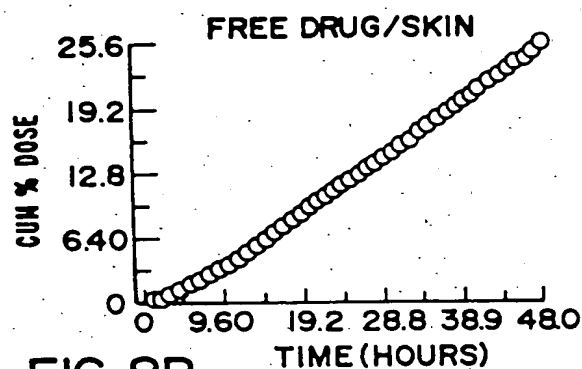
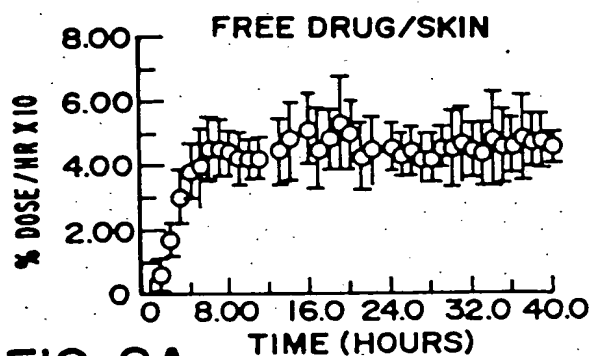
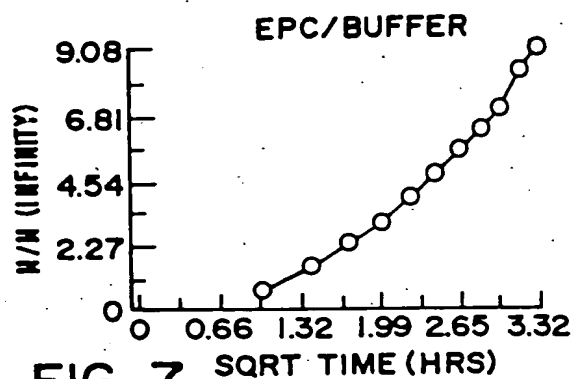
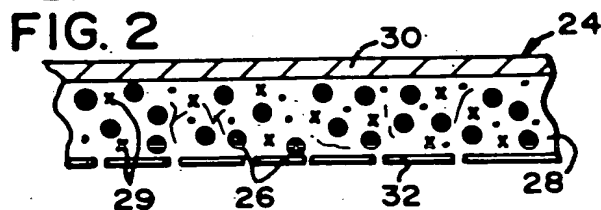
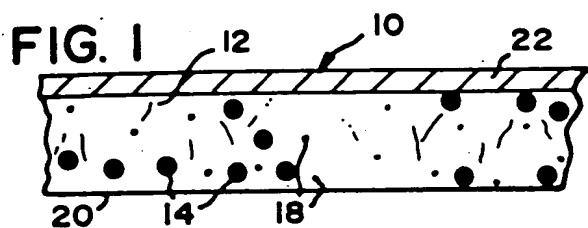
10 13. The method of claim 11, for achieving a relatively low drug release rate, wherein the lipid components are selected to include phospholipids whose acyl-chain moieties are predominantly saturated and/or long-chain.

15 14. The method of claim 11, for use in a drug delivery system containing a hydrophilic drug in the matrix, wherein the lipophilic drug is a drug transport agent effective to facilitate transdermal uptake of the  
20 hydrophilic drug.

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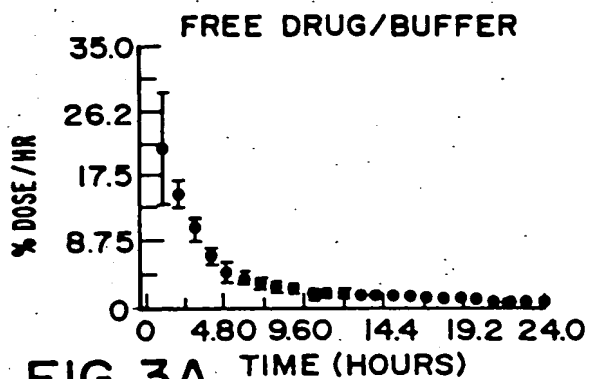


FIG. 3A

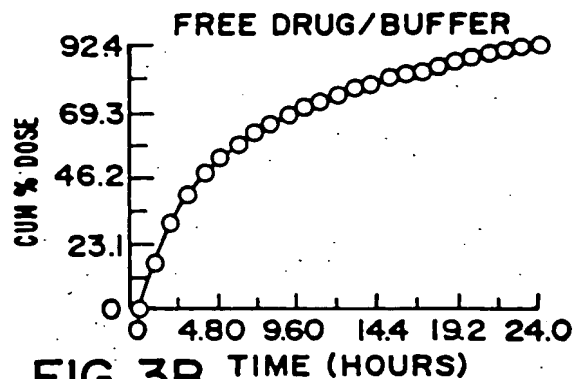


FIG. 3B

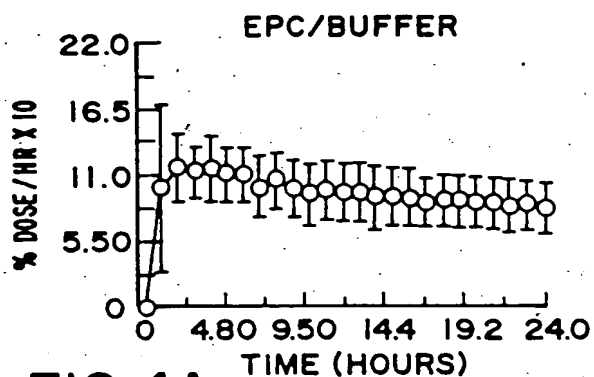


FIG. 4A

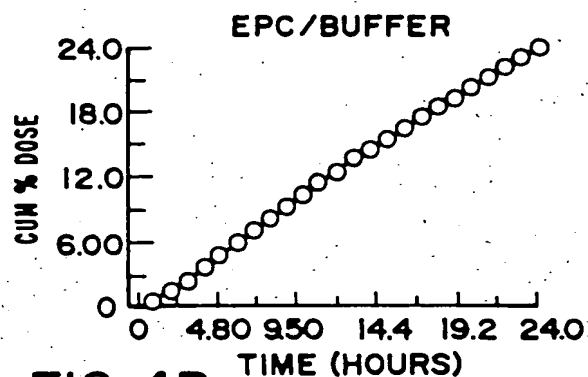


FIG. 4B

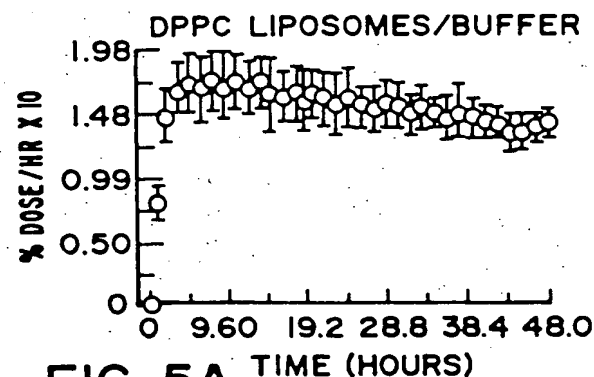


FIG. 5A

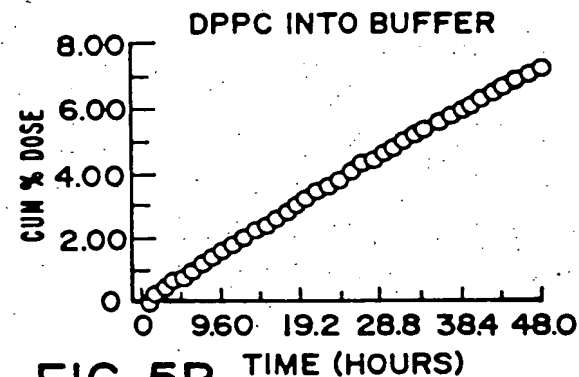


FIG. 5B

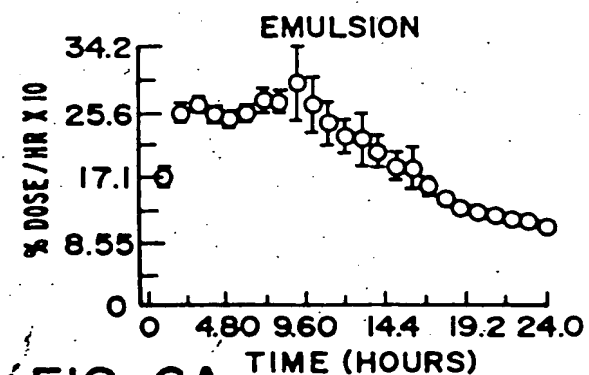


FIG. 6A

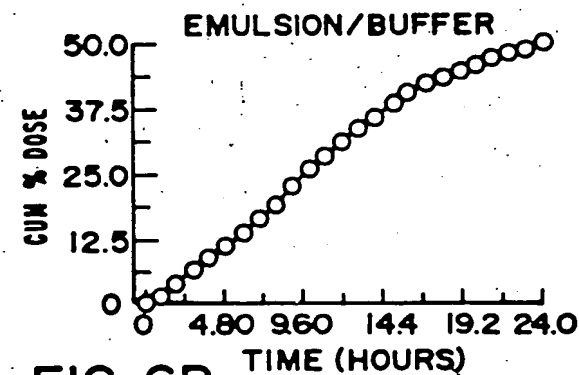
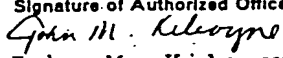


FIG. 6B

SUBSTITUTE SHEET

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/01893

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC INT. CL. (4) A61K 9/42; A61J 5/00; B01J 13/02; B32B 5/16 U.S. CL. 424-38; 264-4.1, 4.3, 4.6; 428-402.2		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
U.S.	424-38 264-4.1, 4.3, 4.6 428-402.2	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> 14		
Category *	Citation of Document, 15 with indication, where appropriate, of the relevant passages 17	Relevant to Claim No. 18
Y	US, A, 3,598,123 (ZAFFARONI) 10 August 1971, see the entire document.	ALL
Y	US, A, 3,989,816 (RAJADHYAKSHA) 02 November 1976, see col. 1, line 60 - col. 2, line 21.	ALL
Y	US, A, 3,797,494 (ZAFFRONI) 19 March 1974, see the entire document.	ALL
Y	US, A, 4,286,592 (CHANDRASEKARAN) 01 September 1981, see the entire document.	ALL
Y	US, A, 4,316,893 (RAJADHYAKSHA) 23 February 1982, see col. 1, line 61- col. 2, line 29.	ALL
Y	Chemical Abstracts, Volume 102, No. 9, issued 04 March 1985 (Columbus, Ohio, USA), Krowczynski, "Liposomes as Drug Carriers in Transdermal Therapy," see page 355, the abstract No. 102:84351a, Pharmazie. 1984, 39(9), 627-9 (Ger).	ALL
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: 15</p> <p>"A" document defining the general state of the art</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document cited for special reason other than those referred to in the other categories</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> </div> <div style="width: 45%;"> <p>"P" document published prior to the international filing date but on or after the priority date claimed</p> <p>"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search *	Date of Mailing of this International Search Report *	
20 November 1986	03 DEC 1986	
International Searching Authority *	Signature of Authorized Officer 20	
ISA/US	 John M. Kilcoyne	

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

P, Y

Chemical Abstracts, Volume 104, No. 3, issued 20 January 1986 (Columbus, Ohio, USA,) Komatsu, "Preparation of Drug-Liposome Inclusion Compounds", see page 300, the abstract No. 104:24197m, Jpn. Kokai Tokkyo Koho JP 60,152,410 [85, 152,410] 10 August 1985.

ALL

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>10</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ..... because they relate to subject matter <sup>12</sup> not required to be searched by this Authority, namely:

2. ☐ Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out <sup>13</sup>, specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>11</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.